(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 16 August 2001 (16.08.2001)

PCT

(10) International Publication Number WO 01/58956 A3

- (51) International Patent Classification?: C07K 16/24, A61K 39/395, C12N 5/10, 15/13, A61K 38/17, 38/13, 31/505, 31/445, C12N 15/85, A61P 1/00, 3/00, 5/00, 7/00, 9/00, 11/00, 13/00, 15/00, 17/00, 19/00, 21/00, 25/00, 29/00, 31/00, 33/00, 35/00, 37/00, A61K 31/56, 31/56, 31/56 // (A61K 39/395, 31:505) (A61K 39/395, 38:13) (A61K 39/395, 31:445) (A61K 39/395, 31:56) (A61K 39/395, 38:17)
- (21) International Application Number: PCT/US01/04170
- (22) International Filing Date: 9 February 2001 (09.02.2001)
- (25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/181,608

10 February 2000 (10.02.2000) U

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US

60/181,608 (CON)

Filed on

10 February 2000 (10.02.2000)

- (71) Applicant (for all designated States except US): BASF AKTIENGESELLSCHAFT [DE/DE]; Ludwigshafen, Rheinland-Pfalz (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): GHAYUR, Tariq [PK/US]; 1014 Washington Street, Holliston, MA 01746 (US). DIXON, Richard, W. [US/US]; 6 Samuel Drive, North Grafton, MA 01546 (US). ROGUSKA, Mike [US/US]; 16 Hilldale Road, Ashland, MA 01721 (US). WHITE, Michael [US/US]; 30 Angelica Drive, Framingham, MA 01701 (US). LABKOVSKY, Boris [US/US]; 107A-5 Broadmeadow Road, Marlborough, MA 01752 (US). SALFELD, Jochen [DE/US]; 177 Old

Westboro Road, North Grafton, MA 01536 (US). DUN-CAN, Alexander, Robert [GB/GB]; 8 Garden Fields, Little Shelford, Cambridge CB2 5HH (GB). BROCK-LEHURST, Simon, Mark [GB/GB]; 38 Huntsmill, Fulbourn, Cambridge CB1 5RH (GB). MANKOVICH, John [US/US]; 416 Lowell Street, Andover, MA 01810 (US). SHORROCK, Celia, Patricia [GB/US]; 17 Stanley Road, Cambridge CB5 8LF (GB). THOMPSON, Julia, Elizabeth [GB/GB]; Seeby's Cottage, 6 High Street, Whittlesford, Cambridge CB2 4LT (GB). LENNARD, Simon, Nicholas [GB/GB]; 1 Bakers Lane, Linton, Cambridgeshire CB1 6NF (GB).

- (74) Agents: DECONTI, Giulio, A., JR. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

with international search report

(88) Date of publication of the international search report: 7 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIBODIES THAT BIND HUMAN INTERLEUKIN-18 AND METHODS OF MAKING AND USING

(57) Abstract: Antibodies that bind human interleukin-18 (hIL-18) are provided, in particular antibodies that bind epitope(s) of human IL-18. The antibodies can be, for example, entirely human antibodies, recombinant antibodies, or monoclonal antibodies. Preferred antibodies have high affinity for hIL-18 and neutralize hIL-18 activity in vitro and in vivo. An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. Method of making and method of using the antibodies of the invention are also provided. The antibodies, or antibody portions, of the invention are useful for detecting hIL-18 and for inhibiting hIL-18 activity, e.g., in a human subject suffering from a disorder in which hIL-18 activity is detrimental.



International Application No PCT/US 01/04170

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K16/24 A61K39/395 A61K38/17 C12N15/13 C12N5/10 A61P1/00 C12N15/85 A61K31/445 A61K31/505 A61K38/13 A61P11/00 A61P9/00 A61P7/00 A61P5/00 A61P3/00 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K A61K C12N A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ.

C. DOCUM	NTS CONSIDERED TO BE RELEVANT	Delevent to claim No.
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х	EP 0 974 600 A (HAYASHIBARA BIOCHEM LAB) 26 January 2000 (2000-01-26) paragraph [0021] paragraph [0038] - paragraph [0040] paragraph [0045] - paragraph [0071] claims 1-27	1-3,53, 55,57,59
X	KOHKA HIDEO ET AL: "Involvement of interleukin-18 (IL-18) in mixed lymphocyte reactions (MLR)." JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, vol. 19, no. 9, 1999, pages 1053-1057, XP001007317 ISSN: 1079-9907 the whole document	1,2,53, 55,57, 59,60

X Further documents are fisted in the continuation of box C.	X Patent family members are listed in annex.
Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance.	"T" tater document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filling date but later than the priority date claimed	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "8" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2001	1 7. 09. 01
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Renggli, J

2

PCT/US 01/04170

IPC 7	A61P13/00 A61P25/00 A61P25/00 A61P37/00	A61P15/00 A61P29/00 A61K31/56	A61P17/00 A61P31/00 A61K31/56	A61P19/00 A61P33/00 A61K31/56	A61P21/00 A61P35/00	
According to	International Patent Class	sitication (IPC) or to both	national classification an	d IPC		
B. FIELDS S	EARCHED	tollos	wen by classification symi	oois)		
Minimum doc	cumentation searched (c)	assification system tollow	wed by classification symt			
Documentation	on sourched other than m	notimentation t	o the extent that such doc	ruments are included in t	ne helds searched	
Documentan	on searched other than in	minum document				
			(name of data base and.	where practical, search t	erms used)	
Electronic das	ta base consulted during t	the international search	(Harris or cam case and			
C. DOCUME	NTS CONSIDERED TO E	BE RELEVANT				
Category 1	Citation of document, will	th indication, where app	ropnate, of the relevant pa	assage\$	Relevant to claim	No.
1						
P,X	WO 00 56771	L A (HOLMES S	TEPHEN D		1,2,53,	
	· SMITHY! INF	E REECHAM PLC	(PRI: ARDEL	MEGUID	55,57,59	
	SHERIN) 28 September 2000 (2000-03-20)					
1	page 2 -pag	ge 3; claims	1-23			
1						
-						
İ						
ľ						
Furthe	er documents are asted in	the continuation of box	с. Х	Patent family members	are listed in annex.	
	er documents are listed in			se document published aft	er the international filing date	
* Special cate 'A* documen	egories of cited document	ts:	T late or cr	er document published aft pnonty date and not in co ted to understand the prin		
'Special cate 'A' document	agories of cited document at defining the general state ared to be of particular rele	ts: te of the art which is not evance	T late of	or document published aft priority date and not in cred to understand the prin version	er the international filing date inflict with the application but ciple or theory underlying the ince; the claimed invention	
* Special cate 'A' documen conside 'E' earner do filing da'	egories of cited document at defining the general state ared to be of particular rele acument but published on te	is: te of the art which is not evance or after the internationa	T late or in X do	or document published after phonity date and not in content of the understand the prince purpose of particular relevants to considered nove wolve an inventive step with the content of the union to the considered nove wolve an inventive step with the content of the union to the	er the international tiling date softic with the application but ciple or theory underlying the since; the claimed invention or cannot be considered to the document is taken alone.	
*Special cate "A" documen	egories of cited document at defining the general state red to be of particular rele ocument but published on the and throw doubts crited to establish the pub-	te of the art which is not avance or after the international s on phonity claim(s) or objection date of another	T late of control of c	or document published after priority date and not in cited to understand the printersion current of particular relevations of the considered nove volve an inventive step with the consideral relevations to particular relevations to consideral in inventive to inventive consideral in inventive to inventive considerations.	er the international filing date inflict with the application but ciple or theory underlying the ince: the claimed invention for cannot be considered to the document is taken alone ince: the claimed invention to the invention invention in the invention invention in the invention in the invention in the invention in the internation in	
'A' documen conside 'E' earner do filing da' 'L' documen which is citation	agories of cited document at defining the general state ared to be of particular rela- comment but published on the at which may throw doubts cred to establish the put or other special reason (a not reterring to an oral disci-	is: Ite of the art which is not avance To rafter the international is on phonty claim(s) or bication date of another as specified)	T late on control of the control of	or document published after phonty date and not in content to understand the printers of particular relevation of particular relevation of particular relevation of particular relevation to be considered from the considered to investment of particular relevation to be considered to investment is combined with	er the international tiling date softic with the application but ciple or theory underlying the since; the claimed invention or cannot be considered to the document is taken alone since; the claimed invention over an invention step when the one or more other such docu-	
A documen conside E earner do filing da: "L" documen which is citation of documen other ma	agories of cited document in defining the general sta- ired to be of particular rele- cument but published on the which may throw doubts is cited to establish the pub- or other special reason (a in retering to an oral discleans	ts: te of the art which is not evance or after the internationals on phority claim(s) or obscation date of another as specified) dosure, use, exhibition of	T late or criming or criminal crimin	or document published after priority date and not in cred to understand the print version current of particular relevant to be considered nove volve an inventive step will current of particular relevant to the considered to invocument is combined with ents, such combination but the art.	er the international filing date inflict with the application but ciple or theory underlying the ince: the claimed invention or cannot be considered to be the document is taken alone ince: the claimed invention over an inventive step when the one or more other such docuering obvious to a person skilled	
"A" documen conside "E" earner do filing da: "L" documen which is citation of documen other me."P" documen	agories of cited document at defining the general state ared to be of particular rela- comment but published on the at which may throw doubts cred to establish the put or other special reason (a not reterring to an oral disci-	is: Its of the art which is not evance or after the international is on priority claim(s) or objection date of another as specified) iosure, use, exhibition of ternational filing date but	T late on control of the control of	or document published after priority date and not in coted to understand the priority date and not in coted to understand the priority date and not in current of particular relevants to considered nove wolve an inventive step will current of particular relevants to combined with cents, such combined with the art.	er the international filing date on the international filing date on the particular of the control of cannot be considered to nent the document is taken alone ince; the claimed invention over an inventive step when the occurrence one or more other such document of the claimed invention one or more other such document obvious to a person skilled one patent family	
"A" documen conside "E" earner do filing da: "L" documen which is citation "O" documen other mi"P" documen later tha	agories of cited document in defining the general state red to be of particular rela- ocument but published on the in which may throw doubts is cited to establish the pub- ic reter special reason (a in referring to an oral disclerans in published prior to the ini-	is: te of the art which is not evance or after the international is on phonty claim(s) or objection date of another as specified) diosure, use, exhibition of ternational filling date but d	T late on control of the control of	or document published after priority date and not in cred to understand the print version current of particular relevant to be considered nove volve an inventive step will current of particular relevant to the considered to invocument is combined with ents, such combination but the art.	er the international filing date on the international filing date on the particular of the control of cannot be considered to nent the document is taken alone ince; the claimed invention over an inventive step when the occurrence one or more other such document of the claimed invention one or more other such document obvious to a person skilled one patent family	
"A" documen conside "E" earner do filing da: "L" documen which is creation "O" documen other mi "P" documen later tha	agories of cited document at defining the general state ared to be of particular rele accument but published on the in which may throw doubts a cited to establish the put or other special reason (a in referring to an oral disclerans at published prior to the interesting to the i	is: te of the art which is not evance or after the international is on phonty claim(s) or objection date of another as specified) diosure, use, exhibition of ternational filling date but d	T late on control of the control of	or document published after priority date and not in coted to understand the priority date and not in coted to understand the priority date and not in current of particular relevants to considered nove wolve an inventive step will current of particular relevants to combined with cents, such combined with the art.	er the international filing date on the international filing date on the particular of the control of cannot be considered to nent the document is taken alone ince; the claimed invention over an inventive step when the occurrence one or more other such document of the claimed invention one or more other such document obvious to a person skilled one patent family	
"A" documen conside "E" earner do filing da: "L" documen which is citation "O" documen other mi"P" documen later tha	egories of cited document at defining the general state and to be of particular rele accument but published on the at which may throw doubts acted to establish the pub- cited to establish the pub- c	te of the art which is not evance or after the international is on phonity claim(s) or obication date of another as specified) dosure, use, exhibition of ternational filling date build demational search	T late of or	or document published after priority date and not in coted to understand the priority date and not in coted to understand the priority date and not in current of particular relevants to considered nove wolve an inventive step will current of particular relevants to combined with cents, such combined with the art.	er the international filing date on the international filing date on the particular of the control of cannot be considered to nent the document is taken alone ince; the claimed invention over an inventive step when the occurrence one or more other such document of the claimed invention one or more other such document obvious to a person skilled one patent family	
"A" documen conside "E" earner do filing da "L" documen which is citation "O" documen other ms" "P" documen later tha Date of the ac	egories of cited document at defining the general state and to be of particular rele accument but published on the at which may throw doubts acted to establish the pub- cited to establish the pub- c	te of the art which is not evance or after the international international discussion date of another as specified) dosure, use, exhibition of iternational filling date but discussion date or another as a specified) discussion date of a specified of the specifi	T late of or	er document published after priority date and not in coted to understand the priority date and not in coted to understand the priority date and not in cument of particular relevants to considered nove wolve an inventive step will cument of particular relevants of particular relevants of combined with ents, such combination by the art.	er the international filing date on the international filing date on the particular of the control of cannot be considered to nent the document is taken alone ince; the claimed invention over an inventive step when the occurrence one or more other such document of the claimed invention one or more other such document obvious to a person skilled one patent family	

International Application No PCT/US 01/04170

A. CLASSIF IPC 7	FICATION OF SUBJECT MATTER //(A61K39/395,31:505),(A61K39/395 (A61K39/395,31:56),(A61K39/395,38	,38:13),(A61K39/395,31: :17)	445),
According to	International Patent Classification (IPC) or to both national classific	ation and IPC	
D DEL 00	CEARCHED		
Minimum do	cumentation searched (classification system followed by classification	on Symbols	
	ion searched other than minimum documentation to the extent that	such documents are included in the fields se	arched
Documentat	ion searched direct marrial minimum.		
Electronic da	ala base consulted during the international search (name of data ba	ise and, where practical, search terms used)	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category *	Citation of document, with indication, where appropriate, of the re	levant passages	1,0,0,0,0,0
1			
1			
1			
ļ			
Į			0
1			M)
Fun	ther documents are listed in the continuation of box C.	X Patent family members are listed	in annex.
Special ca	ategories of cited documents:	"T" later document published after the inte or priority date and not in conflict with	the application out
"A" docum	ent defining the general state of the art which is not	cited to understand the principle or th	eory underlying the
l consi	dered to be of particular relevance document but published on or after the international	"X" document of particular relevance; the t	r de considered 10
filing	date	involve an inventive step when the do	cument is taken alone
which	n is cited to establish the publication date of phosts. on or other special reason (as specified)	"Y" document of particular relevance; the cannot be considered to involve an in document is combined with one or many	venive steb when the
O docum	nent reterring to an oral disclosure, use, exhibition or	ments, such combination being obvio	us to a person skilled
"P" docum	rmeans nent published prior to the international filing date but than the priority date claimed	in the art. "8" document member of the same patent	tamily
i	e actual completion of the international search	Date of mailing of the international sea	arch report
1	24 July 2001		
Name and	mailing address of the ISA	Authorized officer	
	European Patent Office, P.B. 5818 Patentiaan 2	2 -1:	
	Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Renggli, J	

2

PCT/US 01/04170

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Although claims 53, 55, 57, 59 and 60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3,53,55,57,59 (part) and 60
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3, 53, 55, 57, 59 (part) and 60

A compound capable of binding a human IL-18 amino acid sequence or portion thereof, wherein said amino acid comprises a sequence selected for the group consisting of SEQ ID NO:67 and SEQ ID NO:68 and methods of inhibiting or treating involving the use of said compound.

2. Claims: 4-10, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

A human monoclonal antibody, or antigen binding portion thereof, capable of binding to human IL-18 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

3. Claims: 11-15, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, comprising an amino acid sequence selected from the group comprising seq ID:3 and 33 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

4. Claims: 16-21, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or antigen-binding portion thereof, that binds to an epitope of human IL-18, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a koff rate constant of 0.1 s-1 or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC50 of 1 x 10-6 M or less and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 22-28, 32-35, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated human antibody, or an antigen-binding portion thereof, comprising at least one variable region CDR domain capable of binding an epitope of human IL-18 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

6. Claims: 29-31, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid sequence selected from the group consisting of seq IDs: 15, 16 and 17 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

7. Claims: 36-38, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid selected from the group consisting of seq IDs: 26, 27 and 29 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

8. Claims: 47-52

A method of making an antibody that binds human interleukin-18 comprising exposing an antibody repertoire to an antigen comprising an epitope of human IL-18 or portion thereof and selecting from the antibody repertoire an antibody that binds the epitope of human IL-18, or potion thereof.

Information on patent family members

International Application No
PCT/US 01/04170

Patent document cited in search report		Patent family member(s)	Publication date
Α	26-01-2000	JP 2000236884 A	05-09-2000
Α	28-09-2000	NONE	
	A	A 26-01-2000	date member(s) A 26-01-2000 JP 2000236884 A